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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/393,590 | 09/09/1999 | ELIZABETH MOYER | 00211-US-NEW | 2967 |

21835 7590 06/01/2004

ELAN PHARMACEUTICALS, INC.
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| EXAMINER | |
|---|---|
| DEVI, SARVAMANGALA J N | |
| **ART UNIT** | **PAPER NUMBER** |
| 1645 | |

DATE MAILED: 06/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/393,590 | MOYER ET AL. | |
| | Examiner | Art Unit | |
| | S. Devi, Ph.D. | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) *29-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *22304*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**Request for Continued Examination**

**1)** A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 02/23/04 has been entered.

**Applicants' Response**

**2)** Acknowledgment is made of Applicants' response filed 02/23/04 in response to the final Office Action mailed 02/26/03.

**Status of Claims**

**3)** No claims have been amended.

Claims 1-58 are pending.

Claims 1-28 are under examination.

**Information Disclosure Statement**

**4)** Acknowledgment is made of Applicants' information disclosure statement filed on 02/23/2004. The information referred to therein has been considered and a signed copy of the same is attached to this Office Action.

**Prior Citation of Title 35 Sections**

**5)** The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

**Prior Citation of References**

**6)** The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

**Rejection(s) Withdrawn**

**7)** The rejection of claims 1-3, 5, 14-17, 21 and 27 made in paragraph 10 of the Office Action mailed 06/05/02 (paper no. 15) and maintained in paragraph 6 of the Office Action mailed 02/26/03 under 35 U.S.C § 102(b) as being anticipated by Schantz *et al.* (*J. AOAC* 61: 96-99,

1978 - Applicants' IDS), is withdrawn in light of the modified rejection made below. Applicant's arguments with respect to this rejection have been considered but are moot in view of the withdrawal of, and the new ground(s) of rejection.

**Rejection(s) under 35 U.S.C § 112, First Paragraph**

**8)** Claims 1-28 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a stable liquid pharmaceutical formulation comprising a purified type B botulinum toxin and a succinate buffer having a pH of 5.6, wherein the liquid formulation is stable for at least one year at a temperature of 5 degrees centigrade, or for at least six months at a temperature of 25 degrees centigrade, does not reasonably provide enablement for a stable liquid pharmaceutical formulation comprising a purified botulinum toxin of any type other than type B and a buffer other than succinate buffer having any pH other than 5.6 or 5.4 within the pH range of about 5 and 6, wherein the formulation is stable as a liquid for at least one year at any temperature other than 5 centigrade within the temperature of about 0 to 10, or for at least six months at any temperature other than 25 degrees centigrade within the temperature range of 10 to 30 degrees centigrade, as claimed broadly.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to the stability of a liquid formulation of various botulinum toxins at broad temperature and pH ranges. The state of the art at the time indicates that botulinum toxins vary in their stability in solvent or liquid form based on the type of buffer used, the pH, and the temperature used for storage. Encompassed in the scope of the claims are stable liquid pharmaceutical formulations of types A, C1, C2, D, E, F and G

botulinum toxins contained in any buffer capable of providing a pH range between about 5 and 6 at a temperature of about 0-10 or about 10-30 degrees centigrade. A review of the specification shows that the only botulinum toxin that has been shown to be stable as a liquid pharmaceutical formulation in a single buffer, succinate buffer, for at least one year at one particular temperature of 5°C and at a pH of 5.6 is botulinum toxin type B present at a concentration of about 2500 Units/ml (see Example 2 and Table 2). Table 3 of the specification demonstrates that the liquid botulinum type B toxin formulation was stable for at least 6 months in succinate buffer at a single temperature of 25°C and a pH of 5.6 or 5.4. Other than this pH, this buffer, and these two specific temperatures, no other pH of the broadly recited pH range of 5 to 6, or no other temperature of the broadly recited temperature range of 0 to 10 degrees centigrade, or 10 to 30 centigrade, were even included in the experiments performed. Other than type B botulinum toxin, no other 'purified' botulinum toxin of any other type, such as, type A, C1, C2, D, E, F or G were evaluated for long-term stability as liquid formulations at any temperature or pH. The stability of the claimed type B toxin liquid formulation within the full concentration range as recited in claims 9, 11-13, 22 and 24-26 is also not enabled. This is critically important because the art reports of lack of clarity and of many contradictions on the subject of stability of botulinum toxins as related to various factors (see first full paragraph on page 57 of Boroff *et al.* (*In*: *Microbial Toxins*. (Ed) Kadis *et al.* Academic Press, New York, 1-62, 1971, already of record). Claims 7 and 20 recite the use of phosphate buffer and phosphate-citrate buffer at the recited temperature and pH ranges. The specification does not provide any evidence that these two buffers at the recited pH and temperature ranges rendered a botulinum toxin liquid formulation of any type stable for as long as 6 months, one year, or two years. With regard to phosphate buffer of pH 6.2 (i.e., about 6.0), the art specifically describes that a botulinum toxin solution was stable at room temperature in this buffer only for a few days, as opposed to months or years (see second full paragraph in left column on page 139 of Gartlan and Hoffman. *Otolaryng. Head Neck Surg.* 108:135-140, 1993, already of record). A review of literature on the storage or shelf life of botulinum toxins indicates that at the time of the invention, no published data existed that documented the stability of the botulinum toxins after reconstitution for more than a few hours (see paragraph bridging pages 135 and 136 of Gartlan and Hoffman, 1993). It was known in the art that nontoxic proteins

associated with botulinum neurotoxins contribute to the stability of the neurotoxins, and that purified neurotoxins, i.e., neurotoxins separated from the protective nontoxic proteins, exhibited poor stability (see last full paragraph on page 44 of Shcantz and Johnson. *In*: *Therapy with Botulinum Toxin*. (Ed) J. Jankovic *et al.* Marcel Dekker, Inc., New York, 41-50, 1994). In the instant application, the only purified botulinum toxin that has been shown to remain stable as a liquid formulation in succinate buffer at a pH of 5.6 and a temperature of 5 or 25 degrees centigrade, is the type B botulinum toxin. There is absolutely no evidentiary showing that this observation or result is extrapolatable to other botulinum toxins, already known and those yet to be discovered, nor is it predictable in light of Boroff's teachings described above. A review of post-filing art also indicates that those of skill in the art have not yet successfully showed that the stability features demonstrated with the BoNT-B or Myobloc liquid formulation are applicable or reproducible with botulinum toxins of other types, such as, type A, C1, C2, D, E, F and G (see Grethlein *et al. Pain Med.* 2: # 203, page 239, 2001). The full scope of the claims is not commensurate with the enabling disclosure. Due to the lack of specific disclosure and/or guidance, the lack of evidence or the lack of working examples enabling the full scope, the associated contradiction/unpredictability factor, the breadth of the instant claims, and the quantity of experimentation necessary, undue experimentation would have been required at the time of the effective filing date of the instant application for one of ordinary skill in the art to reproducibly practice the full scope of the invention, as claimed. The ability to reproducibly practice the full scope of the claimed method is well outside the realm of routine experimentation. The enablement (scope) provisions of 35 U.S.C. § 112, first paragraph, are not met and the claims are viewed as unsupported with respect to their scope.

**Rejection(s) under 35 U.S.C § 102**

**9)** Claims 16, 17, 21 and 27 are rejected under 35 U.S.C § 102(b) as being anticipated by *Schantz et al.* (*J. AOAC* 61: 96-99, 1978 - Applicants' IDS).

The specification does not provide a closed definition for the limitation 'about'. Instead, the specification states that the term 'about' in the context of the claims means 'nearly' or 'approximately'. In the context of numerical values, the specification does not commit the meaning of the term 'about' to a strict numerical definition, i.e., the specification does not require

that the term 'about' *must* be construed to estimate a value that is ± 10% of the value or range recited. In the absence of a limiting or closed definition within the instant specification, the term 'about' in this rejection is given its general interpretation of 'approximately'.

It is noted that the instant specification at lines 18-20 of page 3 describes the term 'room temperature' to encompass the general temperature range of 10-30°.

Schantz *et al.* taught a solvent composition comprising purified botulinum type A toxin in acetate buffer having a pH of 4.2 (i.e., about 5) for at least two years at room temperature. One preferable temperature range taught is 18-24 degrees centigrade (see pages 96 and 97), which is well within the recited temperature range of about 10 and 30 degrees centigrade. The composition further includes gelatin and serum albumin, i.e., excipient protein (see abstract and page 96).

Claims 16, 17, 21 and 27 are anticipated by Schantz *et al.*

**Remarks**

**10)** Claims 1-28 stand rejected.

**11)** Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

**12)** Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. The Examiner can normally be reached on Monday to Friday from 7.45 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

May, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER